Phase II Study of Sequential Triplet Chemotherapy, Irinotecan and Cisplatin Followed by Amrubicin, in Patients with Extensive-Stage Small Cell Lung Cancer: West Japan Thoracic Oncology Group Study 0301

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Introduction: Combination chemotherapy of irinotecan, a topoisomerase I inhibitor, and cisplatin is a standard treatment in patients with extensive-stage small cell lung cancer (SCLC). Amrubicin, a novel 9-aminoanthracycline, inhibits topoisomerase II. We investigated a sequential triplet chemotherapy consisting of irinotecan and cisplatin followed by amrubicin in patients with extensive-stage SCLC.

Methods: Eligible patients were aged 20 to 70 years and had Eastern Cooperative Oncology Group performance status of 0 or 1, measurable lesions, and adequate organ functions. Chemotherapy consisted of irinotecan 60 mg/m^2 on days 1 and 8 plus cisplatin 60 mg/m^2 on day 1 every 3 weeks for three cycles and then amrubicin 40 mg/m^2 alone on days 1 to 3 every 3 weeks for three cycles.

Results: From September 2004 to September 2006, 45 patients were enrolled, 43 were evaluable for response and survival, and 44 were evaluable for toxicity. Twenty-eight patients (64%) completed the full planned chemotherapy. One patient achieved complete response and 33 had partial response for an overall response rate of 79%. Median progression-free survival was 6.5 months. Median overall survival was 15.4 months. Major toxicity was myelosuppression. Grade 3 or 4 neutropenia, anemia, thrombocytopenia, and febrile neutropenia occurred in 57%, 7%, 0%, and 7% of patients during irinotecan/cisplatin cycles and in 91%, 27%, 9%, and 15% of patients during amrubicin cycles, respectively.

Conclusions: The sequential triplet chemotherapy, irinotecan and cisplatin followed by amrubicin, is an effective and well-tolerated treatment in patients with extensive-stage SCLC. Further investigation of this treatment is warranted.

Key Words: Amrubicin, Small cell lung cancer, Sequential chemotherapy, Triplet chemotherapy.

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Small cell lung cancer (SCLC) accounts for approximately 15% of all lung cancers. Disease extension of SCLC is classified as limited stage or extensive stage. Limited-stage SCLC is defined as tumor confined to the hemithorax of origin, the mediastinum, and the supraclavicular lymph nodes, whereas extensive-stage SCLC as tumor spread outside these limits. For extensive-stage SCLC, chemotherapy is the mainstay of treatment. SCLC is highly sensitive to chemotherapy, with a response rate of 70% to 90% in first-line treatment. However, for most patients with extensive-stage SCLC, the disease recurs within several months, and the 5-year survival rate is less than 1%.[1] It is necessary to develop a new treatment for this serious disease.

Irinotecan, a derivative of camptothecin, inhibits topoisomerase I and shows strong antitumor effect for SCLC. The Japan Clinical Oncology Group conducted a randomized phase III trial (JCOG 9511) comparing irinotecan plus cis-

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platin with etoposide plus cisplatin in patients with extensive-stage SCLC.[2] This trial was terminated early, because of a highly statistically significant difference in survival between the two arms. The median overall survival was 12.8 months in the irinotecan/cisplatin arm and 9.4 months in the etoposide/cisplatin arm ($p = 0.002$). In Japan, the combination of irinotecan and cisplatin is recognized as a standard treatment for extensive-stage SCLC.

Amrubicin, a novel 9-aminoanthracycline, inhibits topoisomerase II[3] and also shows strong antitumor effect for SCLC. The West Japan Oncology Group, formerly named the West Japan Thoracic Oncology Group (WJTOG), conducted a phase II study of amrubicin in previously untreated patients with extensive-stage SCLC.[4] In 35 patients treated, a response rate of 76% and a median overall survival of 11.7 months were shown. These figures compare favorably with standard doublet chemotherapy.

Some preclinical studies reported that a combination of topoisomerase I and II inhibitors shows a synergistic cytotoxicity.[5] For SCLC, a combination of this type, irinotecan and etoposide (a topoisomerase II inhibitor), was investigated clinically and showed promising results.[6,7] The similar combination of irinotecan and amrubicin is worthwhile to investigate.

Concurrent administration of a triplet combination requires dose reduction of each drug because of toxicities, especially myelosuppression. A sequential chemotherapy, i.e., a doublet followed by the other drug, can be used to avoid the need for dose reduction. In addition, Norton and Simon[8] presented a theoretical model describing the possibility of a sequential chemotherapy.

Therefore, we investigated a sequential triplet chemotherapy consisting of irinotecan and cisplatin followed by amrubicin in patients with extensive-stage SCLC (WJTOG 0301). The purpose of this study was to evaluate the efficacy and safety of this treatment.

PATIENTS AND METHODS

Patient Selection

Eligible patients were aged 20 to 70 years, had histologically or cytologically proven SCLC, extensive-stage disease, Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 or 1, no prior chemotherapy, neither palliative radiation nor surgery of 14 days, measurable lesions, life expectancy of at least 2 months, and adequate organ functions (white blood cell [WBC] $\geq$4000/μL, neutrophil $\geq$2000/μL, platelet $\geq$100,000/μL, hemoglobin $\geq$10 g/dL, aspartate aminotransferase [AST] and alanine aminotransferase [ALT] $\leq 2 \times$ upper limit of normal [ULN], total bilirubin $\leq 1.5 \times$ ULN, creatinine $\leq$ULN, arterial partial pressure of oxygen $\geq$60 mm Hg, no abnormality requiring treatment on electrocardiogram, and left ventricular ejection fraction on echocardiogram $\geq$60%). Patients with any of the following conditions were excluded: symptomatic brain metastases, pleural or pericardial effusion requiring drainage, interstitial pneumonitis, active infection, watery diarrhea or ileus, active gastroduodenal ulcer, continuous administration of steroid or nonsteroidal anti-inflammatory drug, uncontrolled diabetes mellitus or angina pectoris, other active malignancy, and pregnancy or lactation.

All patients gave written informed consent. This study was approved by the institutional review boards at each participating institution.

Treatment Schedule

Chemotherapy consisted of irinotecan 60 mg/m^2 on days 1 and 8 plus cisplatin 60 mg/m^2 on day 1 every 3 weeks for 3 cycles and then amrubicin 40 mg/m^2 alone on days 1 to 3 every 3 weeks for three cycles. Irinotecan was administered as a 90-minute intravenous infusion, cisplatin as a 90-minute intravenous infusion with adequate hydration, and amrubicin as a 5-minute intravenous injection. Prophylactic administration of granulocyte colony-stimulating factor (G-CSF) was allowed at the discretion of the treating physician.

The minimum requirements for the administration of irinotecan and cisplatin were as follows: WBC $\geq$3000/μL, neutrophil $\geq$1500/μL, platelet $\geq$100,000/μL, AST and ALT $\leq 2.5 \times$ ULN, total bilirubin $\leq 1.5 \times$ ULN, creatinine $\leq$ULN, PS of 0 to 2, body temperature $\leq$37.5°C, no diarrhea, no interstitial pneumonitis, and other nonhematological toxicity $\leq$grade 2. The minimum requirements for administration of day-8 irinotecan were as follows: WBC $\geq$3000/μL, platelet $\geq$100,000/μL, body temperature $\leq$37.5°C, no diarrhea, no interstitial pneumonitis, and other nonhematological toxicity $\leq$grade 2. The minimum requirements for administration of amrubicin were as follows: WBC $\geq$3000/μL, neutrophil $\geq$1500/μL, platelet $\geq$100,000/μL, AST and ALT $\leq 2.5 \times$ ULN, total bilirubin $\leq 1.5 \times$ ULN, creatinine $\leq 1.5 \times$ ULN, PS of 0 to 2, body temperature $\leq$37.5°C, no interstitial pneumonitis, and other nonhematological toxicity $\leq$grade 2.

If any of the following toxicities was observed, the doses of irinotecan, cisplatin, and amrubicin were reduced to 50, 50, and 35 mg/m^2, respectively: WBC $<$1000/μL, febrile neutropenia (neutrophil $<$1000 /μL), platelet $<$25,000 /μL, or grade 3 nonhematologic toxicity. If creatinine $>$ULN, the dose of cisplatin was reduced to 50 mg/m^2. If creatinine $>$2.0 mg/dL, the administration of cisplatin was discontinued. If grade 4 nonhematological toxicity or pneumonitis $\geq$grade 2 was observed, the study treatment was stopped.

Response and Toxicity Evaluation

Before treatment, a complete medical history was obtained, and physical examination was performed. The following examinations were carried out: complete blood count (CBC) with differential WBC count, blood chemistry, arterial blood gas analysis, urinalysis, electrocardiography, and echocardiography. Staging procedures consisted of chest radiograph, computed tomography (CT) of chest and upper abdomen, magnetic resonance imaging (MRI) or CT of brain, bone scintigraphy, and bone marrow aspiration. During treatment, CBC with differential WBC count, blood chemistry, and chest radiograph were examined at least once a week, and electrocardiography and CT and/or MRI for response evaluation were examined once a month. After treatment, chest radiograph was performed once a month, and CT and/or MRI were performed every 3 months.

Response was evaluated according to the Response Evaluation Criteria in Solid Tumors.[9] Extramural review of eligibility and response of all patients were performed. Toxicity was evaluated in accordance with the Common Terminology Criteria for Adverse Events, Version 3.0.[10]

Statistical Analysis

The primary end point of this study was response rate. Secondary end points were progression-free survival (PFS), overall survival, and toxicity. Survival curves were drawn using the Kaplan-Meier method.[11]

Assuming that a response rate of 90% would indicate potential usefulness, whereas a rate of 75% would be the lower limit of interest, with $\alpha = 0.05$ (one side) and $\beta = 0.20$, 38 patients were required. Allowing for a 15% loss to follow-up, enrollment of a total of 45 patients was planned.

RESULTS

Patient Characteristics

From September 2004 to September 2006, 45 patients were enrolled in this study. Two patients had limited-stage disease. One patient, who was able to receive thoracic radiation, was excluded from all analyses. The other patient, who was not able to receive thoracic radiation due to pleural dissemination, was included in analysis of toxicity and excluded from analysis of response and survival. Therefore, 43 patients were evaluable for response and survival, and 44 were evaluable for toxicity.

Patient characteristics are shown in Table 1. The median age was 63 years, 37 patients (84%) were men, and 31 patients (70%) had PS of 1. Thirty-nine patients (89%) had distant metastases. Frequent sites of distant metastases were brain, liver, bone, and adrenal gland. Of five patients without distant metastases, four had contralateral hilar lymph node involvement and one had pleural dissemination. No patient received prior treatment, including surgery and radiation.

TABLE 1. Patient Characteristics ($n = 44$)

Characteristic	*n* (%)
Sex	
Male	37 (84)
Female	7 (16)
Age (yr)	
Median (range)	63 (47–70)
ECOG performance status	
0	13 (30)
1	31 (70)
Distant metastases	
Present	39 (89)
Absent	5 (11)
Sites of distant metastasis	
Brain	10 (23)
Liver	10 (23)
Bone	10 (23)
Adrenal gland	10 (23)
Lymph node	7 (16)
Lung	6 (14)
Bone marrow	3 (7)
Other	3 (7)
Prior therapy	
None	44 (100)

ECOG, Eastern Cooperative Oncology Group.

TABLE 2. Treatment Delivery ($n = 44$)

Treatment Cycle	*n* (%)
Irinotecan/cisplatin	
Cycle 1	44 (100)
Cycle 2	40 (91)
Cycle 3	37 (84)
Amrubicin	
Cycle 1	33 (75)
Cycle 2	30 (68)
Cycle 3	28 (64)

TABLE 3. Tumor Response ($n = 43$)

	n (%)
Complete response	1 (2)
Partial response	33 (77)
Stable disease	1 (2)
Progressive disease	3 (7)
Not evaluable	5 (12)
Overall response	34 (79) (95% CI, 64–90)

CI, confidence interval.

Treatment Delivery

Of 44 patients, 37 patients (84%) received three cycles irinotecan/cisplatin and 28 patients (64%) completed the full planned chemotherapy, i.e., three cycles irinotecan/cisplatin followed by three cycles amrubicin (Table 2). Dose reduction of irinotecan/cisplatin and amrubicin was necessary in six and seven patients, respectively.

Response and Survival

Of 43 patients, 1 achieved complete response and 33 had partial response, for an overall response rate of 79% (95% confidence interval, 64–90%) (Table 3). Of the 33 partial responders, tumor shrinkage met partial response criteria during an irinotecan/cisplatin cycle in 30 patients and during an amrubicin cycle in 3. In the complete responder, tumor disappearance was achieved during an irinotecan/cisplatin cycle.

The survival curves are shown in Figure 1. The median PFS was 6.5 months (95% confidence interval, 4.9–7.4 months), with a 1-year survival rate of 8%. The median overall survival was 15.4 months (95% confidence interval, 11.7–18.0 months), with a 1-year survival rate of 61%.

Chemotherapy After Progression (Second-Line Treatment)

Thirty-five patients received chemotherapy after progression as follows: etoposide plus carboplatin in 10 patients;

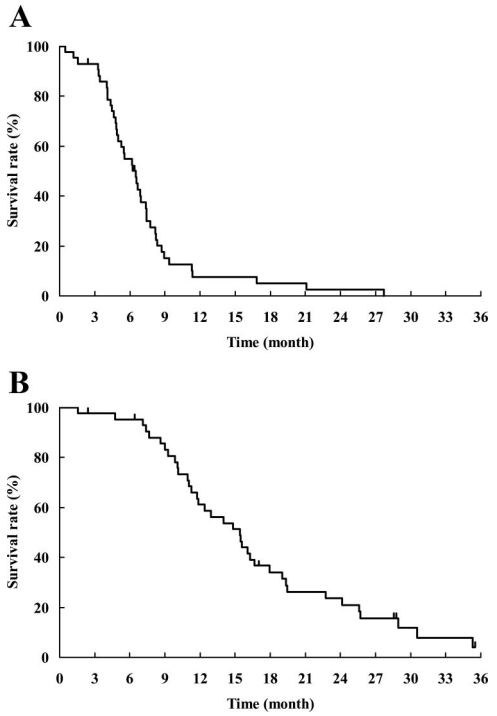

FIGURE 1. Survival curves (n = 43). *A*, Progression-free survival, median 6.5 months (95% confidence interval, 4.9–7.4 months), with a 1-year survival rate of 8%. *B*, Overall survival, median 15.4 months (95% confidence interval, 11.7–18.0 months), with a 1-year survival rate of 61%.

irinotecan plus cisplatin in 6; amrubicin in 5; topotecan plus carboplatin in 4; irinotecan plus amrubicin in 2; irinotecan in 2; and irinotecan plus etoposide, irinotecan plus carboplatin, etoposide plus cisplatin, etoposide, topotecan, and cyclophosphamide plus doxorubicin plus vincristine in 1 patient each.

Toxicity

Toxicities during irinotecan/cisplatin cycles are listed in Table 4. Of 44 patients, grade 3 or 4 leukopenia, neutropenia, anemia, thrombocytopenia, and febrile neutropenia occurred in 6 (14%), 25 (57%), 3 (7%), 0 (0%), and 3 patients (7%), respectively. G-CSF was administered in 12 patients (27%). One patient received transfusion of red blood cell concentrates. One patient (2%) developed grade 3 diarrhea. Grade 3 anorexia was observed in seven patients (16%).

Toxicities during amrubicin cycles are listed in Table 5. Of 33 patients, grade 3 or 4 leukopenia, neutropenia, anemia, thrombocytopenia, and febrile neutropenia occurred in 15 (45%), 30 (91%), 9 (27%), 3 (9%), and 5 patients (15%), respectively. G-CSF was administered in 20 patients (61%). One patient received transfusion of red blood cell concentrates and platelet concentrates, and two other patients received transfusion of red blood cell concentrates. Nonhematological toxicity was not common. One patient (3%) developed grade 3 pneumonitis. This patient was treated with steroid pulse therapy and recovered soon thereafter. No treatment-related death was observed.

TABLE 4. Toxicities During the Irinotecan/Cisplatin Cycle (n = 44)

	Grade					
	0	1	2	3	4	≥3
WBC	11	15	12	4	2	6 (14%)
Neutrophil	9	1	9	20	5	25 (57%)
Hemoglobin	3	23	15	3	0	3 (7%)
Platelet	24	19	1	0	0	0 (0%)
Febrile neutropenia	41	0	0	3	0	3 (7%)
AST/ALT	24	15	3	2	0	2 (5%)
Creatinine	35	7	2	0	0	0 (0%)
Nausea	14	14	12	4	0	4 (9%)
Vomiting	24	11	7	2	0	2 (5%)
Anorexia	11	19	7	7	0	7 (16%)
Fatigue	13	21	8	2	0	2 (5%)
Diarrhea	28	10	5	1	0	1 (2%)
Pneumonitis	44	0	0	0	0	0 (0%)
Infection	39	0	3	2	0	2 (5%)
Rash	37	6	0	1	0	1 (2%)

WBC, white blood cell; AST, aspartate aminotransferase; ALT, alanine aminotransferase.

TABLE 5. Toxicities During the Amrubicin Cycle (n = 33)

	Grade					
	0	1	2	3	4	≥3
WBC	0	3	15	12	3	15 (45%)
Neutrophil	1	0	2	18	12	30 (91%)
Hemoglobin	0	5	19	5	4	9 (27%)
Platelet	13	13	4	0	3	3 (9%)
Febrile neutropenia	28	0	0	5	0	5 (15%)
AST/ALT	25	8	0	0	0	0 (0%)
Creatinine	30	3	0	0	0	0 (0%)
Nausea	18	12	3	0	0	0 (0%)
Vomiting	31	2	0	0	0	0 (0%)
Anorexia	17	12	3	1	0	1 (3%)
Fatigue	10	18	4	1	0	1 (3%)
Diarrhea	31	1	1	0	0	0 (0%)
Pneumonitis	31	1	0	1	0	1 (3%)
Infection	29	0	2	2	0	2 (6%)
Rash	30	2	1	0	0	0 (0%)

WBC, white blood cell; AST, aspartate aminotransferase; ALT, alanine aminotransferase.

DISCUSSION

We performed a phase II study of sequential triplet chemotherapy consisting of irinotecan and cisplatin followed by amrubicin in patients with extensive-stage SCLC and demonstrated a response rate, median PFS, and median overall survival of 79%, 6.5 months, and 15.4 months, respectively. The primary end point of this study was response rate, and the expected and the threshold rates were set 90% and 75%, respectively. The actual response rate in this study (79%) was lower than the expected rate but higher than the threshold. JCOG 9511 reported a response rate, median PFS, and median overall survival of

irinotecan/cisplatin arm of 84%, 6.9 months, and 12.8 months, respectively.[2] Comparing this study with JCOG 9511, the response rate and PFS were similar, whereas overall survival was longer in this study. Taking the longer overall survival into consideration, the results of this study were regarded as promising. There is a possibility that the exclusion of PS 2 patients in this study, which were included in JCOG 9511, could have resulted in the longer overall survival. In addition, we could not find any specific trend that would show prolonged overall survival among second-line treatments.

Two randomized trials that compared irinotecan/cisplatin with etoposide/cisplatin were conducted mainly in North America as confirmation studies of JCOG 9511. One was reported by Hanna et al.[12] and the other was conducted by the Southwest Oncology Group (S0124).[13] Although JCOG 9511 showed survival advantage in the irinotecan/cisplatin arm over the etoposide/cisplatin arm, these North American trials did not show significant difference between the two arms. Irinotecan/cisplatin is a standard chemotherapy for SCLC in Japan, whereas etoposide/cisplatin remains standard in North America. It was reported that the response rate, median PFS, and median overall survival of irinotecan/cisplatin arm were 48%, 4.1 months, and 9.3 months in the trial by Hanna et al. and 60%, 5.7 months, and 9.9 months in S0124, respectively. This study showed better survival than the North American trials. However, great caution is needed when comparing this study with the North American trials. S0124 reported the possibility that inherent genetic differences might exist between the study populations, resulting in divergent outcomes with the same cytotoxic agents.[13] A similar suggestion was made for non-small cell lung cancer.[14] Population-related pharmacogenomics is important because the varied results for the same treatment could be attributed to ethnic differences.

Clinical studies of amrubicin for SCLC had been performed, in both first-line and second-line treatment, entirely in Japan.[15] The WJTOG study in first-line treatment reported a response rate of 76% and median overall survival of 11.7 months.[4] These figures compare favorably with standard doublet chemotherapy. Onoda et al.[16] conducted a phase II study of amrubicin in second-line treatment. They treated 16 patients with refractory disease and 44 patients with sensitive relapsed disease and demonstrated a response rate and median overall survival of 50% and 10.3 months in the refractory group and 52% and 11.6 months in the sensitive group, respectively. Furthermore, the North Japan Lung Cancer Study Group conducted a randomized phase II trial of amrubicin in comparison with topotecan in second-line treatment.[17] That trial showed a response rate and median PFS of 38% and 3.5 months for the amrubicin arm and 13% and 2.2 months for the topotecan arm, respectively. Multivariate analysis revealed that amrubicin has more influence than topotecan on overall survival. Amrubicin is one of the most promising new drugs for the treatment of SCLC.

The ECOG reported a phase III trial of topotecan versus observations after cisplatin and etoposide in extensive-stage SCLC.[18] They showed that four cycles of cisplatin/etoposide induction therapy followed by four cycles of topotecan improved PFS but failed to improve overall survival or quality of life in extensive-stage SCLC. Results of the North Japan Lung Cancer Study Group trial suggested that amrubicin is more effective than topotecan for SCLC. The ECOG trial failed to show survival benefit; however, it did show that amrubicin, instead of topotecan, has potential to lead to better survival in extensive-stage SCLC.

Bozcuk et al.[19] reported a meta-analysis of maintenance/consolidation chemotherapy in the management of SCLC. They analyzed 14 randomized trials, encompassing 2550 patients, and concluded that maintenance/consolidation chemotherapy improves survival in SCLC. Sequential amrubicin was stopped for three cycles in this study. If further cycles of amrubicin as maintenance treatment are given, PFS might be further prolonged.

The major toxicity of sequential amrubicin was myelosuppression, whereas nonhematological toxicity was not common. In the above-mentioned WJTOG study, amrubicin was administered at 45 mg/m^2 on days 1 to 3 as monotherapy.[4] To avoid severe myelosuppression in this study, amrubicin was decreased to 40 mg/m^2 on days 1 to 3 as sequential chemotherapy. This study confirmed that this dose of sequential amrubicin was feasible.

Kaneda et al.[20] reported a phase I study of irinotecan and amrubicin. They administered irinotecan on days 1 and 8 and amrubicin on days 1 to 3. They concluded that this combination was not tolerated because of severe myelosuppression. Although concurrent combination of irinotecan and amrubicin is not tolerable, this study showed that sequential combination of these drugs is tolerable. Irinotecan and amrubicin were administered without G-CSF support in both this study and the study by Kaneda et al.

In conclusion, the sequential triplet chemotherapy of irinotecan and cisplatin followed by amrubicin is an effective and well-tolerated treatment in patients with extensive-stage SCLC. Further investigation of this treatment is warranted.

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REFERENCES

1. Sher T, Dy GK, Adjei AA. Small cell lung cancer. *Mayo Clin Proc* 2008;83:355–367.
2. Noda K, Nishiwaki Y, Kawahara M, et al. Irinotecan plus cisplatin compared with etoposide plus cisplatin for extensive small-cell lung cancer. *N Engl J Med* 2002;346:85–91.
3. Hanada M, Mizuno S, Fukushima A, et al. A new antitumor agent amrubicin induces cell growth inhibition by stabilizing topoisomerase II-DNA complex. *Jpn J Cancer Res* 1998;89:1229–1238.
4. Yana T, Negoro S, Takada M, et al. Phase II study of amrubicin in previously untreated patients with extensive-disease small cell lung cancer: West Japan Thoracic Oncology Group (WJTOG) study. *Invest New Drugs* 2007;25:253–258.
5. Vasey PA, Kaye SB. Combined inhibition of topoisomerases I and II—is this a worthwhile/feasible strategy? *Br J Cancer* 1997;76:1395–1397.
6. Masuda N, Matsui K, Negoro S, et al. Combination of irinotecan and etoposide for treatment of refractory or relapsed small-cell lung cancer. *J Clin Oncol* 1998;16:3329–3334.
7. Kudoh S, Nakamura S, Nakano T, et al. Irinotecan and etoposide for previously untreated extensive-disease small cell lung cancer: a phase II

trial of West Japan Thoracic Oncology Group. *Lung Cancer* 2005;49: 263–269.
8. Norton L, Simon R. The Norton-Simon hypothesis revisited. *Cancer Treat Rep* 1986;70:163–169.
9. Therasse P, Arbuck SG, Eisenhauer EA, et al. New guidelines to evaluate the response to treatment in solid tumors. *J Natl Cancer Inst* 2000;92:205–216.
10. Common Terminology Criteria for Adverse Events, Version 3.0. August 9, 2006. Available at: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/ctcaev3.pdf. Accessed October 5, 2009.
11. Kaplan EL, Meier P. Nonparametric estimation for incomplete observations. *J Am Stat Assoc* 1958;53:457–481.
12. Hanna N, Bunn PA Jr, Langer C, et al. Randomized phase III trial comparing irinotecan/cisplatin with etoposide/cisplatin in patients with previously untreated extensive-stage disease small-cell lung cancer. *J Clin Oncol* 2006;24:2038–2043.
13. Lara PN Jr, Natale R, Crowley J, et al. Phase III trial of irinotecan/cisplatin compared with etoposide/cisplatin in extensive-stage small-cell lung cancer: clinical and pharmacogenomic results from SWOG S0124. *J Clin Oncol* 2009;27:2530–2535.
14. Gandara DR, Kawaguchi T, Crowley J, et al. Japanese-US common-arm analysis of paclitaxel plus carboplatin in advanced non-small-cell lung cancer: a model for assessing population-related pharmacogenomics. *J Clin Oncol* 2009;27:3540–3546.
15. Ettinger DS. Amrubicin for the treatment of small cell lung cancer: does effectiveness cross the Pacific? *J Thorac Oncol* 2007;2:160–165.
16. Onoda S, Masuda N, Seto T, et al. Phase II trial of amrubicin for treatment of refractory or relapsed small-cell lung cancer: Thoracic Oncology Research Group Study 0301. *J Clin Oncol* 2006;24:5448–5453.
17. Inoue A, Sugawara S, Yamazaki K, et al. Randomized phase II trial comparing amrubicin with topotecan in patients with previously treated small-cell lung cancer: North Japan Lung Cancer Study Group Trial 0402. *J Clin Oncol* 2008;26:5401–5406.
18. Schiller JH, Adak S, Cella D, et al. Topotecan versus observation after cisplatin plus etoposide in extensive-stage small-cell lung cancer: E7593—a phase III trial of the Eastern Cooperative Oncology Group. *J Clin Oncol* 2001;19:2114–2122.
19. Bozcuk H, Artac M, Ozdogan M, et al. Does maintenance/consolidation chemotherapy have a role in the management of small cell lung cancer? A metaanalysis of the published controlled trials. *Cancer* 2005;104: 2650–2657.
20. Kaneda H, Kurata T, Tamura K, et al. A phase I study of irinotecan in combination with amrubicin for advanced lung cancer patients. *Anticancer Res* 2006;26:2479–2485.